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Applicant(s) : Wilson *et al.* Examiner: Louise Humphrey

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Title: Methods for Identifying Aptamer Regulators (as amended)

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AMENDMENT AND RESPONSE TO FINAL OFFICE ACTION UNDER 37 C.F.R. § 1.116

This is an Amendment and Response to the Final Office Action having a mailing date of October 28, 2008, which has a shortened statutory period set to expire January 28, 2009, and an extended period set to expire March 28, 2009. Applicants submit herewith a petition for a two-month extension of time for responding to the Action, along with the appropriate extension fee.

Applicants request entry of this Amendment and Response because Applicants do not believe that the finality of this Office Action is proper.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 5 of this paper.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in this application:

Claims 1-126 (cancelled).

Claim 127 (new). A method for identifying an aptamer regulator comprising the steps:

a) contacting a mixture of nucleic acids with a target and a target partner under conditions that disfavor efficient binding between the target and the target partner;

b) partitioning nucleic acids bound to a target-target partner complex from unbound nucleic acids; and

c) retaining the nucleic acids bound to the target-target partner complex,

thereby identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer.

Claim 128 (new). The method of claim 127, wherein the mixture of nucleic acids is a target-specific pool of nucleic acids having high affinity and specificity for the target.

Claim 129 (new). The method of claim 128, wherein the target-specific pool of nucleic acids is diversified.

Claim 130 (new). The method of claim 127, wherein the target partner is immobilized.

Claim 131 (new). The method of claim 127, wherein the method further comprises a negative selection prior to step a).

Claim 132 (new). The method of claim 131, wherein the negative selection comprises the steps:

1) contacting a mixture of nucleic acids with the target partner under conditions that favor specific binding between the nucleic acids and the target partner; and

2) partitioning the bound nucleic acids from the unbound nucleic acids, and retaining the unbound nucleic acids;

wherein the unbound nucleic acids are then contacted with the target and the target partner in step a).

Claim 133 (new). The method of claim 127, wherein the method further comprises the step of removing the retained nucleic acids from the target-target partner complex.

Claim 134 (new). The method of claim 133, wherein the removing is by eluting the nucleic acids with an agonist competitor to the target.

Claim 135 (new). The method of claim 133, wherein the removing is by contacting the bound nucleic acids with excess free target.

Claim 136 (new). The method of claim 127, wherein the method further comprises the step of amplifying the retained nucleic acids and repeating steps a) to c).

Claim 137 (new). The method of claim 127, wherein the method further comprises the step of screening the nucleic acids retained in step c) for a desired functional activity.

REMARKS

Claims 127-137 will be pending after entry of this Amendment and Response. Claims 1-126 have been cancelled.

New Claims

The new claims find support in the application, for example, in paragraphs 27-28, 41-43 and 70-107, and in Figures 8-10. In addition, the new claims are derived from the previously pending claims. Therefore, no new matter has been added by the addition of claims 127-137.

Finality of Office Action

The present Action, which has been made final, is the first Action after the filing of a request for continued examination (RCE).

Applicants submit that the finality of this first Action is improper. M.P.E.P. § 706.07(b) states:

> However, it would not be proper to make final a first Office action in a continuing or substitute application or an RCE where that application contains material which was presented in the earlier application after final rejection or closing of prosecution but was denied entry because (A) new issues were raised that required further consideration and/or search, or (B) the issue of new matter was raised.

In this case, the Amendment and Response filed on June 5, 2008 to the Final Office Action dated February 5, 2008 was not entered, according to the Advisory Action dated July 9, 2008, because it raised new issues that would require further consideration and/or search. Applicants then filed an RCE on August 4, 2008 in order to enter the previously unentered Amendment and Response. Therefore, Applicants submit that the finality of the present Action

is premature. Accordingly, withdrawal of the finality of the present Action is respectfully requested under M.P.E.P. § 706.07(d).

Rejection under 35 U.S.C. § 103(a)

Claims 46-57, 60-64, 66 and 69-111 and 113-126 stand rejected under 35 U.S.C. § 103(a) as being obvious in view of Griffin *et al.* (U.S. Patent No. 5,756,291).

Applicants respectfully disagree.

The Examiner begins her analysis by summarizing Applicants' invention. However, the summary is incomplete. For example, the Examiner's summary of step c) is missing the phrase "under conditions that **disfavor** efficient binding between the target and the target partner or target partner analog or both" (emphasis added).

The claimed invention is directed to methods for identifying aptamer regulators. As stated in paragraph [0041] on page 9 of the specification and illustrated in Figures 8-10, aptamer regulators are aptamers wherein binding of the aptamer to a target regulates (activates or suppresses) binding of the target to a target partner.

Griffin *et al.* ("Griffin") disclose methods for identifying oligomer sequences that specifically bind target molecules. The Griffin methods involve complexation of the target molecule with a mixture of oligonucleotides containing random sequences and sequences that serve as a primer for PCR under conditions wherein a complex is formed with the specifically binding sequences, but not with the other members of the oligonucleotide mixture. The complex is then separated from uncomplexed oligonucleotides and the complexed members of the oligonucleotide mixture are recovered from the separated complex using PCR. The recovered

oligonucleotides may be sequenced. Successive rounds of selection using complexation, separation, amplification and recovery can be employed.

The Griffin method may also include a negative selections step. However, the negative selection step in Griffin is part of a subtraction method for aptamer preparation. Griffin states that one could use a positive/negative selection approach or a negative/positive selection approach. Griffin further states that the subtraction method is advantageous in enhancing the specificity of the aptamer obtained to remove members of the starting oligonucleotide mixture that bind to a second substance from which the target molecule is to be distinguished.

The Examiner summarizes the Griffin method as containing a negative selection, which, in the Examiner's opinion, is similar to steps a) and b) of the claimed invention, and a positive selection, which, in the Examiner's opinion, is similar to steps c), d) and e) of the claimed invention.

Applicants disagree with this characterization. Former steps a) and b) of the claimed method, which are now the subject of a dependent claim, employ a negative selection directed to the target partner. That is, the claimed method retains unbound oligonucleotides, which are oligonucleotides that do not bind the target partner. On the other hand, the negative selection in Griffin is directed to oligonucleotides that bind an undesired substance. That is, the Griffin method retains unbound oligonucleotides, which are oligonucleotides that do not bind the undesired substance. The undesired substance is a substance that is to be distinguished from the target.

Former steps c), d) and e) of the claimed method, which are now steps a), b) and c), employ a positive selection under conditions that **disfavor** binding. Therefore, only aptamers that bind to the target and increase the binding affinity of the target for the target partner will be

identified. On the other hand, the Griffin method employs a positive selection under conditions that **favor** binding. Therefore, only aptamers that bind the target will be identified in the Griffin method.

The Examiner goes on to state that Griffin describes an embodiment that uses multiple selections, and that the complex between thrombin and thrombomodulin is the same as the claimed target complex.

Applicants' claimed invention is directed to methods for identifying aptamer regulators. Applicants do not claim compositions.

One embodiment of the Griffin method uses multiple selections to select an oligonucleotide that binds to a complex between thrombin and thrombomodulin. Column 23, line 66 to column 24, line 13 recites:

> Several approaches may be used to select aptamers that block thrombin's activity towards fibrinogen and the thrombin receptor but do not affect the binding of thrombomodulin and activity towards Protein C. These approaches all involve the use of multiple selections to derive aptamers with highly specific properties. In the first example, a pool of oligonucleotides is subjected to two rounds of selection. The first round involves selecting oligonucleotides that bind to thrombin, the second round involves selecting those oligonucleotides that also bind to a complex between thrombin and thrombomodulin. Aptamers derived from such a dual selection strategy will be directed against regions of thrombin apart from the thrombomodulin binding site and will be unlikely to interfere with thrombomodulin binding and activity against Protein C.

The new (and former) independent claims (and the claims that depend therefrom) are each directed to a method for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer. Therefore, aptamer binding to the target **facilitates** the binding of the target to the target partner. Aptamer regulators bind to a target and facilitate binding of the target to a target partner.

On the other hand, the Griffin reference discloses a method for selecting an aptamer that binds to a **pre-existing** protein complex between thrombin and thrombomodulin. Griffin does not disclose a method for selecting an aptamer that binds to thrombin and facilitates the binding of thrombin to thrombomodulin, which is how an aptamer regulator would function. As stated above, the purpose of the multiple selection method in Griffin is to select aptamers that block thrombin's activity towards fibrinogen and the thrombin receptor, but do not affect the binding of thrombomodulin and activity towards Protein C. This is due to the fact that aptamers derived from such a dual selection strategy will be directed against regions of thrombin apart from the thrombomodulin binding site and will be unlikely to interfere with thrombomodulin binding and activity against Protein C. Therefore, Griffin does not teach a method for identifying an aptamer that binds to a target and facilitates the binding of the target to a target partner.

Also, the Examiner states that Griffin discloses eluting the bound aptamers with an agonist competitor, such as fibrinogen immobilized on a column (column 23, lines 49-51), for further negative selection. Column 23, lines 49-51 recite "[a] negative selection could be performed in a similar manner with a fibrinogen substrate column". Not only does the cited sentence not disclose an elution step, but the entire paragraph in which the cited sentence resides does not disclose an elution step. And there is certainly no disclosure of an elution step using an agonist competitor.

The Examiner also states that Griffin describes a method for identifying aptamers that bind to a target like thrombin and increase the binding of thrombin with its partner, thrombomodulin. Applicants disagree with the Examiner's generalization of Griffin's teaching. The Griffin method is specific for thrombin/thrombomodulin, and is not a general method.

In addition, Applicants disagree with the Examiner's assertion that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the thrombin/thrombomodulin complex aptamer selection method by the negative-positive aptamer selection so that only the unbound oligonucleotides from the first round are used in the second round of selection and the thrombin/thrombomodulin complex-bound oligonucleotides are retained.

Applicants disagree with the Examiner's assertion above because it would render Griffin unsatisfactory for its intended purpose. The purpose of the multiple selection method in Griffin is to select aptamers that block thrombin's activity towards fibrinogen and the thrombin receptor, but do not affect the binding of thrombomodulin and activity towards Protein C. If Griffin were to employ a negative selection process in this method, the negative selection would select aptamers that do not bind thrombin or aptamers that do not bind the thrombin/thrombomodulin complex. Each of these outcomes defeat the purpose of the Griffin method, which is to select aptamers that bind to a target (in this case, thrombin).

Secondly, even if the Griffin method is modified according to the Examiner's suggestion, the modified method would, at best, only disclose a method for identifying an aptamer that binds to a **pre-existing** protein complex between thrombin and thrombomodulin. On the other hand, the claimed invention is directed to methods for identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for a target partner and thus facilitates the formation of a target-target partner complex. Therefore, modifying the Griffin method according to the Examiner's suggestion does not render the claimed methods obvious.

Applicants also disagree with the Examiner's statement that the skilled artisan would have been motivated to develop complex-favoring aptamers that function as an agonist that delivers the therapeutic ligand to the specific desired receptor and enhances the binding between the ligand and the receptor. How could the skilled artisan find motivation when Griffin does not teach agonist activity or the concept of an aptamer regulator?

Furthermore, Applicants disagree with the Examiner's assertion that there would have been a reasonable expectation of success given the general protocol of aptamer negative-positive selection protocol with suggested variations to obtain desired aptamers and the teaching that a wide variety of materials can serve as targets. Applicants note that there is a big difference between identifying an aptamer and identifying an agonist aptamer. Very few agonist aptamers exist. Even if one identifies an aptamer that binds to a target, very few aptamers have the additional property of agonist activity. Applicants note that the Griffin method is a single or two step process used to identify an aptamer that binds to a target, wherein, according to the Examiner, agonist activity or the property of increasing binding affinity in the aptamers, may be determined after the disclosed selection during the evaluation of the final product. On the other hand, the method of the invention is a multi-step method that identifies aptamer regulators, *i.e.*, aptamers that bind to a target wherein binding of the aptamer to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer. Simply put, the Griffin method may identify an agonist aptamer or an aptamer regulator by chance, which property would be assessed after the selection method, whereas the method of the invention drives the selection process to identify an agonist aptamer or aptamer regulator from the outset.

The Examiner has also responded to some of Applicants' arguments that were made in responses to previous Office Actions.

First, the Examiner states that Applicants have not provided any evidence showing that an aptamer binding to a pre-existing complex between thrombin and thrombomodulin would not facilitate the binding, and that Applicants have not presented any reasoning to show nonobviousness.

Why would one try to identify an aptamer that facilitates binding between two compounds when the two compounds already exist in a complex?

Applicants also point out that, according to the patent statutes, Applicants are entitled to a patent unless the Office proves that the subject matter is unpatentable. Therefore, the burden of proof is on the Office to prove unpatentability. The burden of proof is not on Applicants to prove patentability. It is not Applicants' burden to prove a negative; it is the Examiner's burden to find and cite art that discloses relevant features of the claimed invention. Here the Examiner is saying, with no supporting evidence, that the cited art achieves the same result as the claimed invention.

Second, the Examiner states that because the selection steps in Griffin are similar to the claimed method steps, one skilled in the art would expect the same result. Applicants admit that there are some similarities between the Griffin method and the claimed method. However, the claimed method utilizes steps that are not found in the Griffin methods. In particular, the claimed method utilizes conditions that disfavor binding. Griffin does not disclose this. In fact, Griffin discloses the opposite.

Third, the Examiner states that Griffin discloses general approaches involving the use of multiple selections to derive aptamers with specific properties, and that the method is not limited by the specific examples set forth in Griffin.

Applicants disagree. For the reasons stated above, Applicants submit that the multiple selection method of Griffin does not render obvious the claimed methods. In addition, the functional selection method in Griffin is specific for thrombin and thrombomodulin. The method is used to select aptamers that block thrombin's activity toward fibrinogen and the thrombin receptor but do not affect the binding of thrombomodulin and activity toward Protein C. This method can not be generalized for broader application because Griffin is selecting for aptamers that bind thrombin in a specific location. For the sake of argument, if the Griffin method were generalized for broader application, at best it would disclose a method for selecting aptamers that bound to a target, but did not bind the target in a ligand binding site. Even this broader application of Griffin does not render obvious the claimed method because the claimed method is directed to a method for identifying an aptamer regulator, which is an aptamer that facilitates binding of a target to a target partner. Griffin, at best, only discloses binding to a target in a specific location, but does not disclose the facilitation of binding between two molecules.

The Examiner also states that even though the aptamer identification method does not select for exactly the same property as the claimed invention, it would be obvious to one skilled in the art at the time to modify the functional selection methods by variations with the target in each binding step and the product in the retaining step to identify aptamers with the desired property.

Applicants disagree. What variations with the target? What modifications are obvious and why are they obvious? Rejections on obviousness can not be sustained with mere

conclusory statements. There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. The key to supporting any rejection under 35 U.S.C. § 103 is the clear articulation of the reasons why the claimed invention would have been obvious. M.P.E.P. §§ 2142 and 2143.

In addition, the Examiner disagrees with Applicants' assertion that Griffin does not describe eluting the bound aptamers with an agonist competitor. The Examiner states that Griffin discloses elution in col. 30, lines 29-31. Assuming, arguendo, that the Examiner is correct, Griffin does not disclose elution with an agonist competitor. Griffin does not discuss the use of an agonist competitor.

The Examiner further states that Griffin, in column 29, lines 17-27, provides the general guideline of complexation under favoring conditions, followed by complexation under disfavoring conditions.

Applicants disagree. The example cited by the Examiner describes the negative/positive selection approach to the subtraction method for aptamer preparation. The subtraction method for aptamer preparation is used to identify aptamers that bind to a target, but do not bind to a second substance from which the target molecule is to be distinguished. In that example, the negative selection is performed first to mix the original oligonucleotide mixture with the undesired substance to complex away the members of the mixture that bind to the second (undesired) substance. That is, any oligonucleotide that binds to the second substance will be eliminated, and only oligonucleotides that do not bind to the second substance will be used to bind to the target in the subsequent positive selection step. Aptamers that bind the target but not the second (undesired) substance will then be identified. Both the negative and positive selection steps are performed under conditions that favor binding. None of the steps in Griffin can be

interpreted as using conditions that disfavor binding. As stated previously, the claimed invention utilizes a step that disfavors binding in order to identify aptamer regulators, which are aptamers that bind to a target and increase the binding of the target for the target partner.

The Examiner also states that Griffin was offered for disclosing an obvious variant of the claimed method with different selection conditions. However, the question, as it relates to patentability, is whether the claimed invention is nonobvious in view of the art, and not whether the art is an obvious variant of the claimed method.

The Examiner notes Applicants' statement that Griffin may identify agonist aptamers by chance, which, according to the Examiner, contradicts Applicants' assertion of the lack of a reasonable expectation of success. Applicants disagree. If a result only happens by chance, then how could there be a reasonable expectation of success?

Furthermore, the Examiner states that features upon which Applicants' rely (aptamer regulators) are not recited in the claims. Applicants disagree with this statement because the independent claim recites, at the end of the claim, the phrase: "thereby identifying an aptamer that binds to a target wherein binding of the aptamer to the target increases the binding affinity of the target for the target partner relative to the affinity of the target for the target partner when the target is not bound by the aptamer."

Finally, the Examiner states that the claimed invention does not distinguish from the prior art selection method steps and does not contain specific limitations, such as specific conditions favoring and disfavoring complex formation, that are crucial for the claimed property selection method. Applicants disagree because new claim 127 (and former independent claims 46, 47, 66 and 114), and the claims that depend therefrom, uses a contacting step with conditions that **disfavor** efficient binding between the target and target partner, whereas the Griffin method does

not. This step helps identify aptamer regulators, *i.e.*, aptamers that **facilitate** binding between the target and target partner. Including such a step in the Griffin method would render the Griffin method unsatisfactory for its intended purpose of identifying aptamers that specifically bind target molecules. In addition, a person having ordinary skill in the art would be familiar with the conditions that favor and disfavor binding, which would vary depending upon the target and target partner. Therefore, including such limitations in the claim is not necessary.

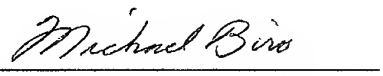
Accordingly, applicants submit that the cited reference does not render obvious the claimed invention. Accordingly, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

Applicants submit that the claims are not obvious in view of the cited reference. Accordingly, reconsideration of the rejection and allowance of the claims at an early date are earnestly solicited.

If there are any questions regarding this Amendment and Response or if the undersigned can be of assistance in advancing the application to allowance, please contact the undersigned at the number set forth below.

Respectfully submitted,



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